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(54) Title: METHOD OF INHIBITING METASTASES OF CANCER CELLS

(57) Abstract

The present invention relates to a method of inhibiting the metastases of cancer cells using a combination of radiation therapy and a matrix metalloproteinase–2 inhibitor, or a combination of a chemotherapeutic agent and a matrix metalloproteinase–2 inhibitor.

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METHOD OF INHIBITING METASTASES OF CANCER CELLS

FIELD OF THE INVENTION

This invention relates to a method of inhibiting the metastases of cancer cells using a combination of radiation therapy and a matrix metalloproteinase-2 inhibitor, or a combination of a chemotherapeutic agent and a matrix metalloproteinase-2 inhibitor.

BACKGROUND OF THE INVENTION

Metastases of cancer cells are a main cause of mortality and treatment failure in cancer patients. Biologically, metastasis is a complex process that can be largely considered as comprising 3 phases: (a) detachment of tumor cells from a tumor, penetration of the detached cells through basement membrance, and invasion of the cells into blood or lymphatic vessels; (b) travel of the detached cells in the circulation to distant sites in the body; and (c) penetration of the cells through vessel walls and other tissue barriers, and growth of the cells at a new site in the body.

Matrix metalloproteinases (MMPs) play a role in metastases of cancer cells. MMPs are a family of proteins of that act to degrade extracellular matrix, which is a main component of basement membrance. Matrix metalloproteinase-2 (MMP-2) is found in many tissues and tumor cells. MMP-2 degrades type IV collagen and fibronectins.

In particular, the expression of human MMP-2, also known as Gelatinase A or type IV collagenase, is upregulated by p53, which is the protein expressed by the p53 tumor suppressor gene. We have recently discovered that MMP-2 is upregulated by wildtype p53, but not mutant p53. In about 50% of human cancers, p53 mutations have occurred that attenuate or inhibit the ability of p53 to regulate MMP-2 activity. In the other 50% of human cancers that have wildtype p53, p53 promotes tumor metastases by increasing MMP-2 expression. It is well-known that p53 can be induced by radiation and chemotherapeutic drugs

(Kastan MB, Canman CE, Leonard CJ, p53, cell cycle control, and apoptosis: implications for cancer. Cancer metastasis Rev 1995;14:3-15). Therefore, in situations where p53 is induced, such as when a patient is treated with a DNA damaging chemotherapeutic agent or radiation, MMP-2 expression is increased, which in turn promotes metastases. In other words, in tumors having wildtype p53, but not those with mutant p53, radiation promotes metastases through the induction of p53, followed by increased expression of MMP-2. Indeed, in patients with nasopharyngeal carcinoma, a cancer where p53 mutation is a rare event, radiation therapy has induced a high rate of metastases.

Therefore, for patients whose tumors contains wildtype p53, chemotherapy and/or radiation therapy should be given in combination with a MMP-2 inhibitors to prevent or attenuate the metastases of cancer cells.

SUMMARY OF THE INVENTION

The present invention provides a method of inhibiting the metastases of cancer cells in a patient having cancer in which wildtype p53 is predominantly expressed, the method comprising administering to a patient having cancer a therapeutically effective amount of a matrix metalloproteinase-2 inhibitor in combination with a therapeutically effective amount of x-ray or gamma radiation.

In a preferred embodiment, the radiation is x-ray radiation.

In another preferred embodiment, the radiation is gamma radiation.

In another preferred embodiment, the MMP-2 inhibitor is administered to the patient prior to exposure to the radiation.

In another preferred embodiment, the MMP-2 inhibitor is administered to the patient concurrently with the radiation.

Also provided is a method of inhibiting the metastases of cancer cells in a patient having cancer, the method comprising administering to a patient having cancer in which wildtype p53 is predominantly expressed, a therapeutically effective amount of a MMP-2 inhibitor in combination with at least one additional chemotherapeutic agent.

In a preferred embodiment, the MMP-2 inhibitor is administered to the patient prior to the administration of the chemotherapeutic agent.

In another preferred embodiment, the MMP-2 inhibitor is administered to the patient concurrently with the chemotherapeutic agent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of inhibiting the metastases of cancer cells in a patent having cancer in which wildtype p53 is predominantly expressed, the method comprising administering to a patient having cancer a therapeutically effective amount of a matrix metalloproteinase-2 inhibitor in combination with a therapeutically effective amount of x-ray or gamma radiation.

As used herein the term "metastases" means the process by which cancerous cells moves from one location in an organism to another.

Whether a cancer expresses wildtype p53 can be determined by detection of the wildtype p53 gene in human cancer tissues. In general, there are two commonly used methods to determine if wildtype or mutant p53 is present in human cancer tissues.

The first method involves immunohistochemical staining for the p53 protein. This method is known and set forth by Sheu L., Chen A., Tseng H., Leu F., Lin J., Ho K., Meng C., "Assessment of p53 Expression in Nasopharyngeal Carcinoma", Human Pathology 1995;26:380-6. Specifically, sections 4 μm thick were cut from the formalin-fixed, paraffin-embedded specimens and placed on gelatin-coated slides. After being heated at 65°C for 60 minutes, the tissue sections were deparaffinized in xylene for 5 minutes, three times each. The sections were rehydrated in graded alcohol and rinsed in Tris-Buffered Saline (TBS). Normal rabbit serum (diluted as 1:5 in TBS) was used as a blocking reagent. The sections were incubated with the wildtype p53-specific monoclonal antibody (pAb1620, Oncogene Science) for 90 minutes followed by biotin-labeled rabbit immunoglobulin antimouse (Dako) and streptavidin-biotin complex linked to alkaline phosphatase (Dako). Slides were washed in TBS three times for 5 minutes each time. The color was developed in naphthol phosphate-

new solution (Dako) after which the slides were slightly counterstained with hematoxylin and mounted.

Another procedure for determining the presence of wildtype p53 in a cancer involves single strand conformation polymorphism (SSCP), and polymerase chain reaction (PCR)-direct sequencing for p53 mutation. Most p53 mutations (95%) found in human cancers are clustered in the center of p53 molecule (DNA binding domain) encoded by exons 5 to 9. The lack of p53 mutations in this region will indicate the wildtype p53 status in the tissue tested. Since the human p53 gene sequence is available, primers can be designed to flank each exon and polymerase-chain reaction will be performed to amplify each exon. SSCP analysis consists of 2 steps: (1) PCR amplification in a total volume of 12.5 µL in the presence of 35S-dATP (Amersham). The reaction mixture (for 30 reactions) consists of 1.125 µL of dATP (10 mM); 7.5 µL of each of 10 mM dGTP, dTTP, and dCTP; 37.5 µL of 10X PCR buffer 22.5 µL of each primer (20 pmol/µL); 4.5 mL a-35S-dATP; 4.5 µL Taq polymerase (Perkin Elmer); and 110 µL dH_2O. The reaction mixture (7.5 µL) was then aliquoted into each tube containing 5 µL of template DNA (20 ng/µL). PCR amplification was performed for 35 cycles at 95°C (30 seconds), 60°C (30 seconds), 72°C (1 minute), and finally for 10 minutes extension at 72°C. After PCR, 6 µL of stop buffer (USB sequencing kit) was added. The amplified fragment was denatured at 98°C for 5 minutes and loaded onto MDE (Hydrolinkgel by AT Biochem, Malvern, PA) containing 10% glycerol and run for 15 hours at 10W. The gel was then dried and exposed to x-ray film for 1 to 2 days. Using human placenta DNA as a positive control, any shifted band in the gel will indicate a p53 mutation. To define the mutated codon, PCR-direct sequencing can be performed as described in the following publications.

See, for example, Sun Y., Hegamyer G., Colburn N.H., "A Simple Method Using PCR for Direct Sequencing of Genomic DNA From Frozen Tumor Tissue Embedded in Optimal Cutting Temperature Compound," BioTechniques 1992;12:639-640; Sun Y., Hegamyer G., Colburn N.H., "PCR-Direct Sequencing of a GC-Rich Region by Inclusion of 10% DMSO: Application to Mouse c-jun," BioTechniques 1993;15:372-374 which are hereby incorporated by reference.

The phrase "predominantly expressed" with regard to p53 means that more wildtype p53 is expressed than mutant p53.

Cancers that can be treated using the combination therapy disclosed herein are cancers in which wildtype p53 is predominantly expressed. Examples of specific cancers that can be treated include, but are not limited to, endometrial, prostate, pancreatic, lung, breast, head, neck, ovarian, gastric, bladder, cervical, colorectal, brain, esophageal, and nasopharyngeal cancer.

The MMP inhibitor of the present invention is a selective MMP-2 inhibitor. A selective MMP-2 inhibitor inhibits MMP-2 to a greater degree than it inhibits any other known MMP inhibitor. Preferably, the MMP-2 inhibitor inhibits MMP-2 two-fold more than it inhibits any other known MMP. More preferably, the MMP-2 inhibitor inhibits MMP-2 ten-fold more than any other MMP. Selective MMP-2 inhibitors may be determined by those skilled in the art by comparing the IC_{50}s of a compound for the various known MMPs. The procedures for determining MMP inhibition for each known MMP are well-known to those skilled in the art. The known MMPs are MMP-1 (interstitial collagenase), MMP-8 (neutrophil collagenase), MMP-13 (collegenase-3), MMP-3 (stromelysin-1), MMP-10 (stromelysin-2), MMP-7 (matrilysin), MMP-11 (stromelysin-3), MMP-9 (gelatinase-B), MMP-12 (metalloelastase), and MMP-14 (MT-MMP).

Examples of known MMP-2 inhibitors include:

[{4-N-hydroxyamino}-2R-isobutyl-3S-{thienyl-thiomethyl}succinyl]-L-phenylalanine-N-methylamide;

(S)-4-dibenzofuran-2-yl-4-oxo-2-(toluene-4-sulfonylamino)-butyric acid;

(S)-2-(dibenzofuran-3-sulfonylamino)-3-methyl-butyric acid; and

4-Hydroxyimino-4-(4'-methyl-biphenyl-4-yl)-butyric acid.

Other MMP-2 selective MMP inhibitors are known. (See, for example, Tamura Y. et al., J. Med. Chem., 1998;41:640-649 and Porter J. et al., Bioorganic & Medicinal Chemistry Letters, 1994;4(23):2741-2746, which are both hereby incorporated by reference.)

The administration of radiation to a patient having cancer is well-known in the art. The present invention concerns the administration of a combination of

radiation and a MMP-2 inhibitor. The MMP-2 inhibitor should be administered to the patient so that inhibition of MMP-2 is occurring while radiation is being administered. Thus, it may be necessary to administer the MMP-2 inhibitor prior to exposure with radiation. One skilled in the art will readily be able to determine the time and amount of administration of the MMP-2 inhibitor by consulting the pharmacokinetic and pharmacodynamic profiles of the particular MMP-2 inhibitor. In addition, the MMP-2 inhibitor can be administered during radiation therapy as well as for a period after radiation therapy. The goal of the administration of the MMP-2 inhibitor is to provide for the inhibition of MMP-2 while radiation is occurring. Typically, the radiation is x-ray or gamma radiation. Those skilled in the art are familiar with radiation therapy for cancer and will readily be able to deliver such therapy.

Similarly, when an MMP-2 inhibitor is administered in combination with at least one additional chemotherapeutic agent, the MMP-2 inhibitor may be administered before the administration of the additional chemotherapeutic agents. Again, it is important that the MMP-2 inhibitor is administered such that MMP-2 is inhibited while the additional chemotherapeutic agents are being administered. In addition to being administered prior to the additional chemotherapeutic agents, the MMP-2 inhibitor can also be administered during the administration of the additional chemotherapeutic agents, and administration of the MMP-2 inhibitor can be continued after the cessation of administration of the additional chemotherapeutic agents. As in the case of a combination of radiation therapy and a MMP-2 inhibitor, those skilled in the art can readily determine the dosage and time of administration required from the pharmacokinetic and pharmacodynamic profile of the particular MMP-2 inhibitor.

The additional chemotherapeutic agents that can be use in combination with a MMP-2 inhibitor include any chemotherapeutic agents used by those skilled in the art for the treatment of cancer. Examples of such chemotherapeutic agents include, but are not limited to the following:

Antimetabolites

folate antagonists

methotrexate

trimetrexate

pyrimidine antagonists

fluorouracil

fluorodeoxyuridine

CB3717

azacitidine

purine antagonists

mercaptopurine

thioguanine

tiazofurin

chlorodeoxyadenosine

pentostatin

sugar modified analogs

cytarabine

fludarabine

ribonucleotide reductase inhibitors

hydroxyurea

Covalent DNA Binding Drugs

nitrogen mustards

aziridines

alkane sulfonates

nitrosourea

platinum compounds

monoalkylating agents,

Noncovalent DNA Binding Drugs

Anthracyclines

daunorubicin

doxorubicin

idarubicin

mitoxantrone

dactinomycin

bleomycin

plicamycin

Inhibitors of Chromatin Function

topoisomerase inhibitors

epipodophyllotoxins

etoposide

teniposide

amsacrine

camptothecin

microtubule inhibitors

vinca alkaloids

vinblastine

vincristine

vindesine

taxol

Drug Affecting Endocrine Function

glucocorticoids

estrogens

antiestrogens

progestins

androgens

antiandrogens

LHRH (GnRH) antagonists

aromatase inhibitors

adrenocortical suppressors

A therapeutically effective amount is an amount of a MMP-2 inhibitor, that in combination with radiation or an additional chemotherapeutic agent inhibits or ameliorates the metastases of cancer cells.

The MMP-2 inhibitors and additional chemotherapeutic agents of the present invention can be administered to a patient either alone or a part of a pharmaceutical composition. The compositions can be administered to patients either orally, rectal, parenterally (intravenously, intramuscularly, or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragées, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body

temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The MMP-2 inhibitors and additional chemotherapeutic agents can be administered as pharmaceutically acceptable salts, esters, amides, or prodrugs. The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively nontoxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as nontoxic ammonium, quaternary ammonium and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, S. M. Berge, et al., "Pharmaceutical Salts," J. Pharm. Sci., 1977;66:1-19 which is incorporated herein by reference.)

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1-C_6alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5-C_7cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1-C_4alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1-C_6alkyl amines and secondary C_1-C_6dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-C_3alkyl primary amines, and C_1-C_2dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

In addition, the MMP-2 inhibitors or additional chemotherapeutic agents of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The MMP-2 inhibitors or additional chemotherapeutic agents of the present invention can exist in different stereoisomeric forms by virtue of the presence of asymmetric centers in the compounds. It is contemplated that all stereoisomeric forms of the compounds, as well as mixtures thereof including racemic mixtures, form part of this invention.

The MMP-2 inhibitors or additional chemotherapeutic agents of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 1,000 mg per day. For a normal human adult having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg/kg of body weight per day is preferable. The specific dosage used, however, can vary. For example, the dosage can depended on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

In addition, it is intended that the present invention cover compounds made either using standard organic synthetic techniques, including combinatorial chemistry, or by biological methods, such as through metabolism.

CLAIMS

What is claimed is:

1. A method of inhibiting the metastases of cancer cells in a patient having cancer in which wildtype p53 is predominantly expressed, the method comprising administering to a patient having cancer a therapeutically effective amount of a matrix metalloproteinase-2 inhibitor in combination with a therapeutically effective amount of x-ray or gamma radiation.

2. The method of Claim 1 wherein the radiation is x-ray radiation.

3. The method of Claim 1 wherein the radiation is gamma radiation.

4. The method of Claim 1 wherein the MMP-2 inhibitor is administered to the patient prior to exposure to the radiation.

5. The method of Claim 1 wherein the MMP-2 inhibitor is administered to the patient concurrently with the radiation.

6. A method of inhibiting the metastases of cancer cells in a patient having cancer, the method comprising administering to a patient having cancer in which wildtype p53 is predominantly expressed, a therapeutically effective amount of a MMP-2 inhibitor in combination with at least one additional chemotherapeutic agent.

7. The method of claim 6 wherein the MMP-2 inhibitor is administered to the patient prior to the administration of the chemotherapeutic agent.

8. The method of Claim 6 wherein the MMP-2 inhibitor is administered to the patient concurrently with the chemotherapeutic agent.

INTERNATIONAL SEARCH REPORT

Interr ˋal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K41/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 07481 A (MERCK & CO INC ;HAGMANN WILLIAM K (US); KOPKA IHOR E (US)) 14 April 1994 see page 7, line 29 - page 8, line 8 see page 2, line 32 see page 24, line 31 - page 25, line 8	1-8
X	US 5 672 583 A (CHAPMAN KEVIN ET AL) 30 September 1997 see column 3, line 18 - line 21; claims see column 3, line 48 - line 53	1-8
X	WO 94 25434 A (CELLTECH LTD ;MORPHY RICHARD JOHN (GB); MILLICAN ANDREW THOMAS (GB) 10 November 1994 see page 24, line 16 - line 26; claims	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 127, no. 3, 21 July 1997 Columbus, Ohio, US; abstract no. 32825, KAYAGAKI, NOBUHIKO ET AL: "Method and agent for inhibiting Fas ligand release and quantitation of cell surface Fas ligand" XP002091613 see abstract & JP 09 124510 A (SUMITOMO ELECTRIC INDUSTRIES, LTD., JAPAN) ---	
A	J. R. PORTER ET AL.: "Potent and selective inhibitors of Galatinase-AQ +. Hydroxamic acid derivatives" BIOORG. MED. CHEM. LETT. (1995), 5(20), 2441-6 CODEN: BMCLE8;ISSN: 0960-894X, vol. 4, no. 22, 1994, pages 2741-2746, XP002091611 cited in the application see abstract; table 2 ---	1-8
P,A	YOSHINORI TAMURA: "Highly selective and orally active inhibitors of Type IV Collagenase (MMP-9 aand MMP-2) : N-Sulfonylamino Acid Deivatives." JOURNAL OF MEDICINAL CHEMISTRY, vol. 41, 1998, pages 640-649, XP002091612 WASHINGTON US cited in the application see abstract -----	1-8

1

INTERNATIONAL SEARCH REPORT

In ational application No.
PCT/US 98/22284

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 1-8 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...rmation on patent family members

Intern... ...al Application No
PCT/US 98/22284

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9407481 A	14-04-1994	AU 5292193 A	26-04-1994
		US 5629343 A	13-05-1997
US 5672583 A	30-09-1997	AU 679474 B	03-07-1997
		AU 5612994 A	22-06-1994
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